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## **Recovery of renal function after long-term dialysis in hemolytic uremic syndrome**

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## Recovery of renal function after long-term dialysis in hemolytic uremic syndrome

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**Abstract** Long-lasting recovery of renal function of the native kidneys after prolonged renal replacement therapy is rare. An 8-year-old girl and a 3-year-old boy had suffered from acute atypical and diarrhea-associated hemolytic uremic syndrome (HUS), respectively, with subsequent apparent end-stage renal failure. Both recovered renal function after long-lasting anuria and dialysis of 8 and 16 months, respectively. After prolonged follow-up, i.e., 7 and 5 years after cessation of dialysis, they attained normal or slightly reduced renal function (plasma creatinine 84 and 90  $\mu\text{mol/l}$ , respectively). In addition, growth and cognitive development were normal. We conclude that caution is appropriate before offering early renal transplantation to pediatric patients with presumed end-stage kidney disease secondary to HUS.

**Keywords** Hemolytic uremic syndrome · Renal replacement therapy · Recovery

### Introduction

The term end-stage kidney disease is used to indicate irreversible kidney failure requiring dialysis and renal transplantation. Recovery of renal function of the native or transplanted kidneys after prolonged dialysis has rarely

been reported, and mainly in adult patients [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. We report on two children with hemolytic uremic syndrome (HUS) [11] who experienced a long-lasting recovery of renal function after being on dialysis for 8 and 16 months, respectively.

### Case reports

Between 1970 and 2002, 130 and 67 patients underwent chronic renal replacement (i.e., necessary renal replacement therapy for more than 6 months) in Zurich and Bern, respectively. In both centers, HUS was an important cause of end-stage renal failure: 12 patients (9%) from Zurich had HUS, two had diarrhea-related HUS and 10 atypical HUS. In Bern, HUS was the underlying cause in five (7%) patients, one had diarrhea-related HUS and four atypical HUS. Two of the 197 patients, both with HUS, recovered renal function.

#### Case 1

An 8-year-old girl with a history of vomiting, fever and pallor for 10 days was referred. There was no history of diarrhea. Physical examination revealed high blood pressure (132/102 mmHg; 95th centile for gender, age and height: 115/75), pallor and a mild scleral jaundice. Hematology showed anemia (hemoglobin 37 g/l, normal 100–150 g/l) and thrombocytopenia ( $85 \times 10^9/\text{l}$ , normal  $200\text{--}400 \times 10^9/\text{l}$ ); a blood film demonstrated moderate red blood cell fragmentation. Blood chemistry disclosed renal failure with elevated creatinine (399  $\mu\text{mol/l}$ , normal range for age  $<66 \mu\text{mol/l}$ ) and urea (54 mmol/l, normal  $<8.2 \text{ mmol/l}$ ), hyperbilirubinemia (45  $\mu\text{mol/l}$ , normal  $<30 \mu\text{mol/l}$ ) and high lactate dehydrogenase (1,360 U/l, normal  $<500 \text{ U/l}$ ). Complement C3, factor H and von Willebrand cleavage protease were normal, antinuclear or antineutrophil cytoplasmic autoantibodies were not detected and the direct Coombs test was negative. Specific *Escherichia coli* lipopolysaccharide antibodies were not measured. Urinalysis showed hematuria, red cell casts and marked proteinuria. No *E. coli* strains harboring genes for shigatoxin were cultured from the stool. Hence the diagnosis of atypical (diarrhea-negative) HUS was made. A renal biopsy was not done. Within 10 days, the girl became anuric. Continuous automated peritoneal dialysis was started, amlodipine was given to treat hypertension and fresh frozen plasma was administered on 15 occasions. During the following 4 weeks she experienced focal seizures with a tendency towards generalization. Intravenous diazepam and phenytoin were given repeatedly, followed by oral carbamazepine. One month after onset of the disease the girl was switched from peritoneal dialysis to hemodi-

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alysis (three sessions per week) because of two episodes of bacterial peritonitis. She continued to be anuric.

Six months after starting dialysis, the girl reported to pass small portions of urine one to two times a week. One month later, urine production increased and hemodialysis was reduced to two weekly sessions. Eight months after onset, dialysis was finally stopped. The subsequent clinical course was uneventful.

Recently, i.e., 7 years after cessation of dialysis, the girl was well on treatment with irbesartan 300 mg daily, chlorthalidone 25 mg daily, and carbamazepine 1,200 mg daily. Growth (body weight: 52 kg, height: 1.64 m) and cognitive development were both normal. Renal function, as assessed as plasma creatinine (84  $\mu\text{mol/l}$ , normal range for age <98  $\mu\text{mol/l}$ ) and estimated glomerular filtration rate (Schwartz formula: 78 ml/min/1.73 m<sup>2</sup> body surface area), was normal. In addition, casual blood pressure (109/50 mmHg; 95th centile: 128/83 mmHg) and 24-h ambulatory blood pressure (108/62 mmHg; 95th centile: 124/76 mmHg), and urinalysis (normal sediment, albumin/creatinine 3.5 g/mol) were normal. No further family members were suffering from HUS or renal disease.

## Case 2

A 3-year-old boy presented with a 5-day history of pallor and several blue bruises. A week earlier he had suffered from watery diarrhea for 2 days after the consumption of raw cow milk. Physical examination demonstrated high blood pressure (120/66 mmHg; 95th centile: 109/65 mmHg), mild scleral jaundice and swollen eyelids. Hematology revealed anemia (hemoglobin 59 g/l) and thrombocytopenia ( $123 \times 10^9/\text{l}$ ); a blood film showed marked red blood cell fragmentation. Blood chemistry disclosed mild renal failure (creatinine 103  $\mu\text{mol/l}$ , normal range for age <51  $\mu\text{mol/l}$ ; urea 14 mmol/l), hyperbilirubinemia (53  $\mu\text{mol/l}$ ) and high lactate dehydrogenase (1,034 U/l). Complement C3 was normal, antinuclear or antineutrophil cytoplasmic autoantibodies were not detected and the direct Coombs test was negative. Specific *E. coli* antibodies were not measured. Urinalysis revealed hematuria, red cell casts and marked proteinuria. *E. coli* strains harboring genes for shiga toxin could not be cultured from his stool at this stage. Systolic blood pressure further increased up to 140–160 mmHg, requiring intravenous administration of dihydropyridine. Several packed red cells had to be given due to persistent microangiopathic hemolytic anemia. A renal biopsy disclosed extensive lesions of thrombotic microangiopathy including both intraglomerular capillaries and extraglomerular arterioles and small arteries. Urinary output decreased and the boy became anuric. Despite the unusual course—slow progression of renal failure over 3 weeks—a presumptive diagnosis of diarrhea-positive HUS was made.

Hemodialysis had to be started 18 days after admission. In addition, plasma exchange with albumin and an infusion of fresh frozen plasma at the end of each session was applied on 12 occasions. As renal function did not improve, plasma exchange was stopped and the patient switched to automated peritoneal dialysis (duration: 12 h during the night; filling volume: 40 ml/kg body weight; number of exchanges: 12/night). Blood pressure control was only achieved with a triple therapy of atenolol, nifedipine and minoxidil.

After being on a constant peritoneal dialysis regimen for 14 months, the boy started to pass urine. Firstly, there were only small volumes once a week, but urine output increased steadily. Finally, 16 months after onset of renal replacement therapy, peritoneal dialysis was ceased.

Recently, i.e., 5 years after cessation of dialysis, the boy was in good health. Growth (body weight: 28 kg, height: 1.31 m) and cognitive development were both normal. Renal function, as assessed as plasma creatinine (90  $\mu\text{mol/l}$ , normal range for age <75  $\mu\text{mol/l}$ ) and estimated glomerular filtration rate (Schwartz formula: 58 ml/min/1.73 m<sup>2</sup> body surface area), was slightly reduced. There was mild microhematuria, but no proteinuria. Despite antihypertensive treatment with valsartan and amlodipine (20 and 7.5 mg daily, respectively), blood pressure (casual: 127/

83 mmHg; 24-h ambulatory: 128/83 mmHg) remained persistently above the 95th centile (casual: 116/77; 24-h: 117/75). Echocardiography and fundoscopy were normal. No further family members were suffering from HUS or renal disease.

## Discussion

We report long-lasting recovery of renal function after prolonged dialysis, i.e., more than 6 months, in pediatric hemolytic uremic syndrome. The term end-stage kidney disease denotes irreversible deterioration of renal function. A few patients, mainly adults, have been reported to regain independent renal function of their native kidneys after long-term dialysis [1, 2, 3, 4, 5, 7, 8, 9]. Recovery mostly occurred within 6–12 months of initiating renal replacement therapy and was generally partial, both related to glomerular and tubular function. In addition, recovery appeared to be more common in kidney diseases secondary to treatable malignancies, adverse effects of drugs as reported in two cases of atypical HUS [2, 4] or in hypertensive kidney disease [1, 9].

Recovery after long-term dialysis has occasionally been reported in children [6, 10]: The duration of renal replacement therapy had lasted less than 1 year in the majority of these children. In addition, the recovery was transient and lasted less than 1 year in the majority of patients.

Which protective factors might have contributed to the favorable outcome in our patients with HUS are not clear, especially as two main risk factors of bad outcome in HUS [12]—long-term anuria in both patients and extensive thrombotic microangiopathy in one—were present. In particular, atypical HUS carries a substantial risk for end-stage renal failure and is an important cause of end-stage renal failure in childhood [11]. The high risk of recurrence—associated with high morbidity and mortality—has prompted some centers, including our own, to avoid early renal transplantation in those children.

In conclusion the present report suggests that caution is appropriate before offering early renal transplantation to pediatric patients with presumed end-stage kidney disease secondary to diarrhea-associated or atypical HUS.

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